Target Proteinuria

Endothelin-1 (ET-1) and Angiotensin II (ANG II) in IgA Nephropathy (IgAN)

EDUCATIONAL PRESENTATION

This module is intended for Healthcare Professionals (HCPs)

MED-HQ-SPT-2300018 | September 2023

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Endothelin-1 (ET-1) and Angiotensin II (ANG II) in IgA Nephropathy (IgAN)

The pathophysiologic actions of ET-1 and ANG II

ET-1 and ANG II interactions

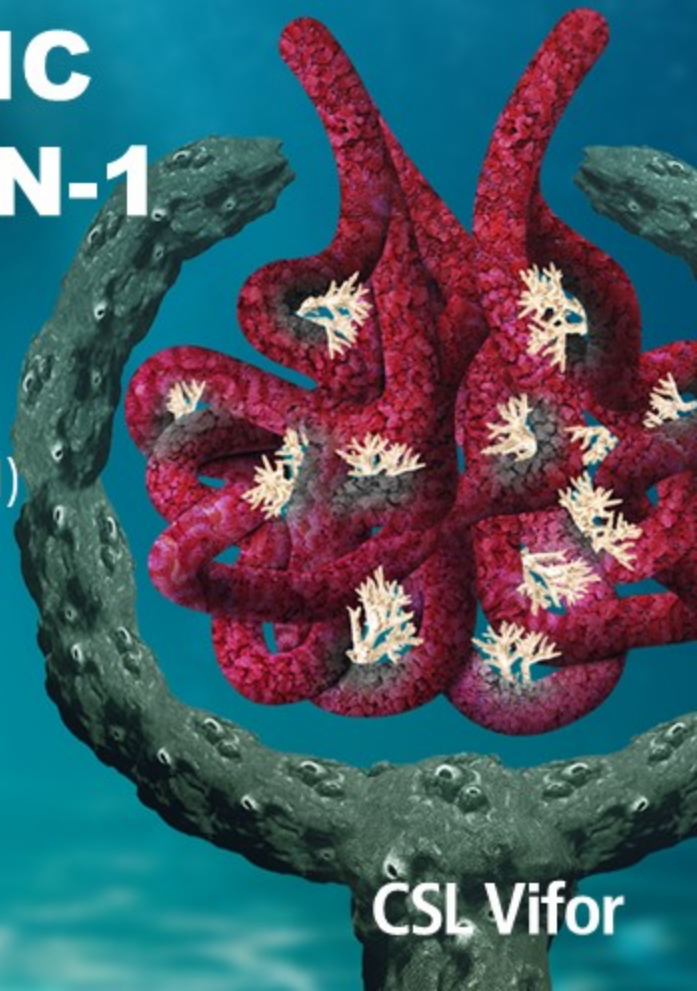
The combined effect of ET-1 and ANG II

ANG II, angiotensin II; ET-1, endothelin-1.

Target Proteinuria

THE PATHOPHYSIOLOGIC ACTIONS OF ENDOTHELIN-1 AND ANGIOTENSIN II

Endothelin-1 (ET-1) and Angiotensin II (ANG II) in IgA Nephropathy (IgAN)



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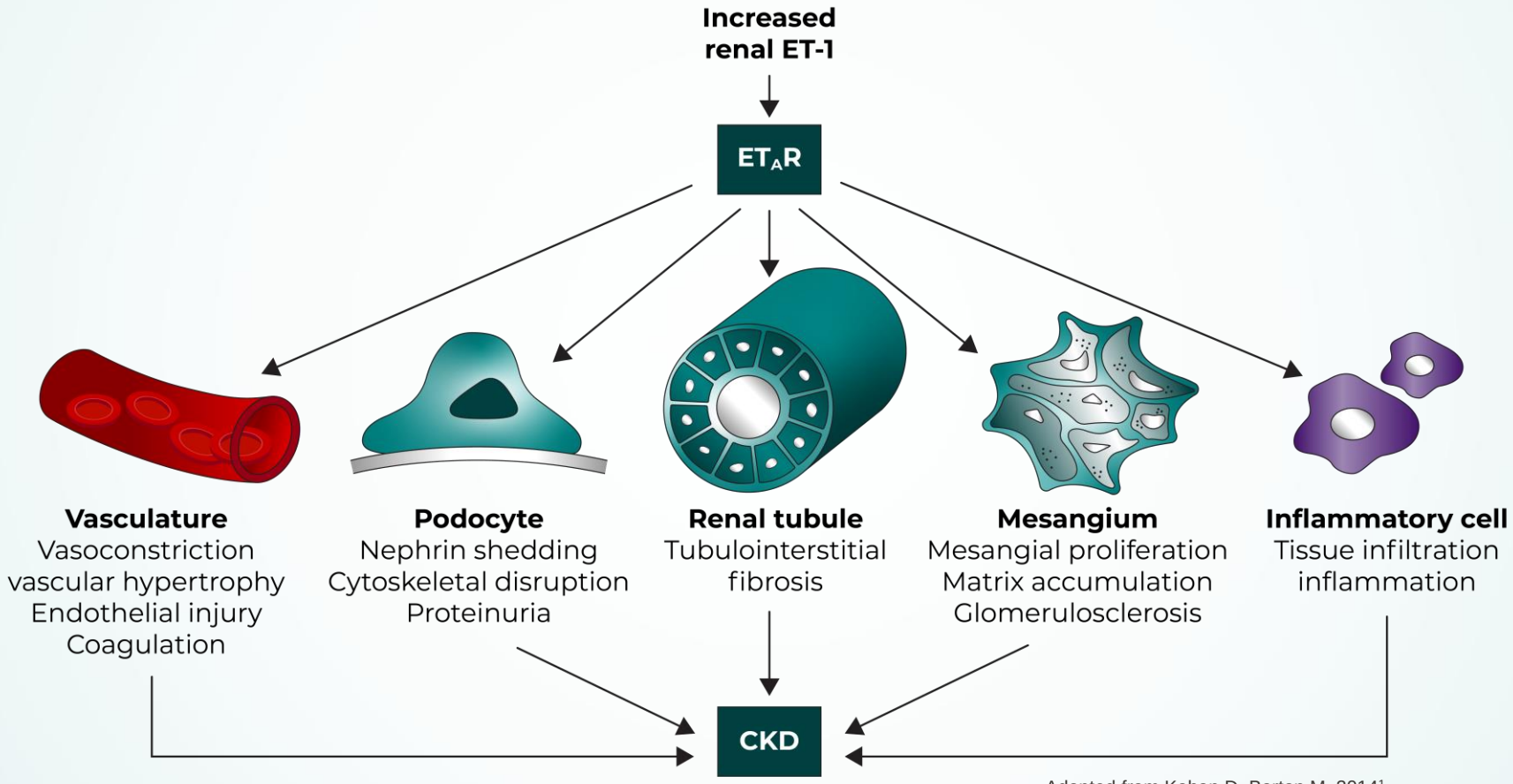
ET-1 HAS PATHOPHYSIOLOGIC EFFECTS ON KIDNEY FUNCTION[1]

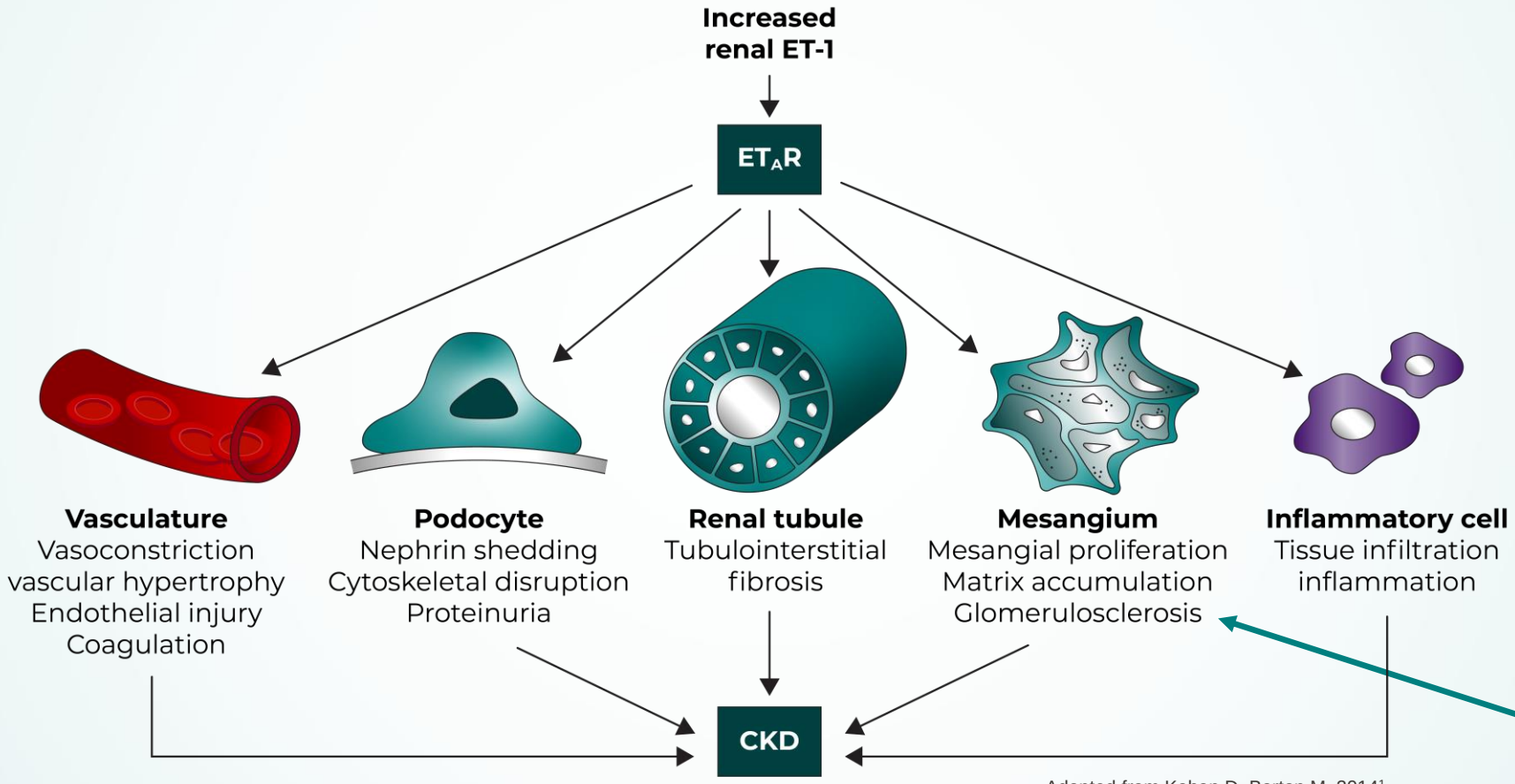


Adapted from Kohan D, Barton M. 2014[1]

CKD, chronic kidney disease; ET-1, endothelin-1; ET_AR, endothelin receptor type A

1. Kohan D, Barton M. *Kidney Int* 2014;86:896–904.

ET-1 HAS PATHOPHYSIOLOGIC EFFECTS ON KIDNEY FUNCTION IN IgA NEPHROPATHY (IgAN)



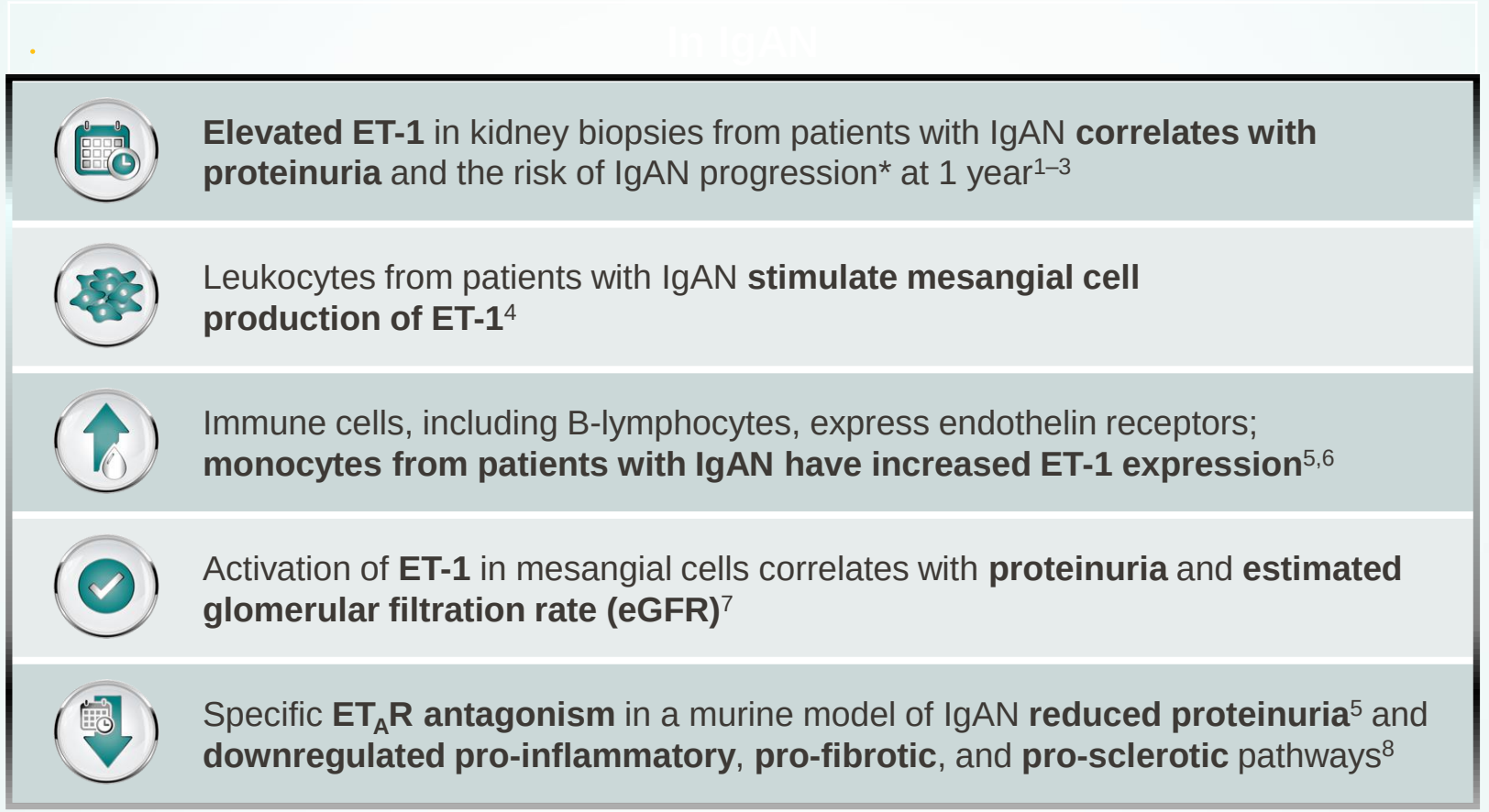
Adapted from Kohan D, Barton M. 2014[1]

IgAN: ET-1 in mesangial cells causes proliferation, contraction, and increased extracellular matrix production[2]

CKD, chronic kidney disease; ET-1, endothelin-1; ET_AR, endothelin receptor type A; IgAN, immunoglobulin A nephropathy

1. Kohan D, Barton M. *Kidney Int* 2014;86:896–904; 2. Barton M, Sorokin A. *Semin Nephrol* 2015;35:156–67.

STUDIES SUGGEST ET-1 HAS A PATHOPHYSIOLOGIC ROLE IN IgAN



*Patients in whom serum creatinine at 12 months increased for more than 20% of baseline values, or in whom the disease proceeded to ESKD, were classified as progressors
eGFR, estimated glomerular filtration rate; ET-1, endothelin-1; ET_AR, endothelin receptor type A; IgAN, immunoglobulin A nephropathy
1. Zanatta C, *et al. Ren Fail* 2012;34:308–15; **2.** Lehrke I, *et al. J Am Soc Nephrol* 2001;12:2321–9; **3.** Tycová I, *et al. Physiol Res* 2018;67:93–105; **4.** Chen H, *et al. Nephron* 2001;89:274–9;
5. Nakamura T, *et al. Lancet* 1993;342:1147–8; **6.** Elisa T, *et al. J Immunol Res* 2015;2015:147616; **7.** Nair V, *et al.* ASN 2021; poster presentation (PO1593); **8.** King A, *et al.* WCN 2021; poster presentation (POS-378).

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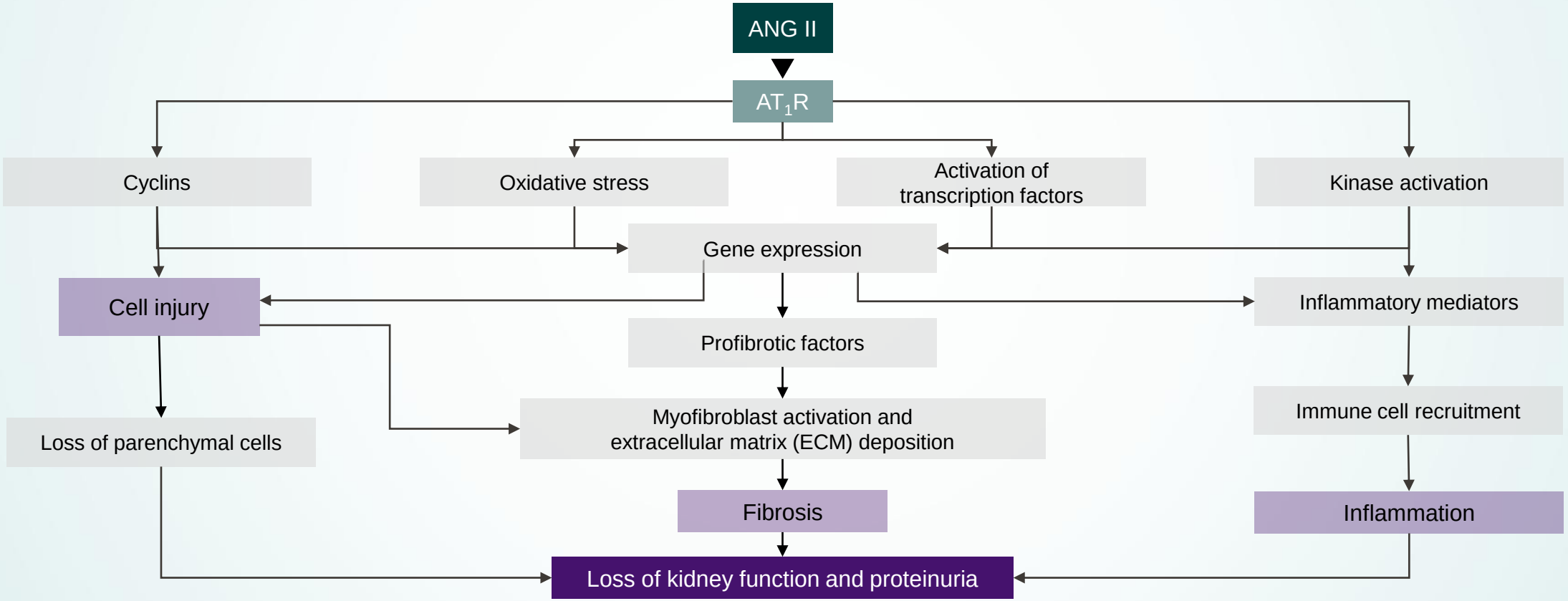
ANG II HAS PATHOPHYSIOLOGIC EFFECTS ON KIDNEY FUNCTION

The role of renin-angiotensin system inhibition in slowing progressive kidney disease is widely appreciated[1,2]



Adapted from Ruiz-Ortega M, *et al*. 2020[2]

ANG II, angiotensin II; AT_1R, angiotensin II receptor type 1; ECM, extracellular matrix

1. Siragy H, Carey R. *Am J Nephrol* 2010;31:541–50; **2.** Ruiz-Ortega M, *et al. Nat Rev Nephrol* 2020;16:269–88.

STUDIES SUGGEST ANG II HAS A PATHOPHYSIOLOGIC ROLE IN IgAN

Purified pIgA induced the synthesis and **secretion of ANG II from human mesangial cells** in patients with IgAN[1]

ANG II-mediated activation of **inflammatory pathways** in mesangial cells was present with **elevated proteinuria*** and blood pressure[2]

AT_1R inhibition has been shown to **mitigate mesangial cell proliferation**,[3] partially reverse **podocyte damage**,[4] **lower proteinuria,** and reduce **inflammation and fibrosis** in the glomerulus and tubulointerstitial compartment[2,5]

*>1g/day

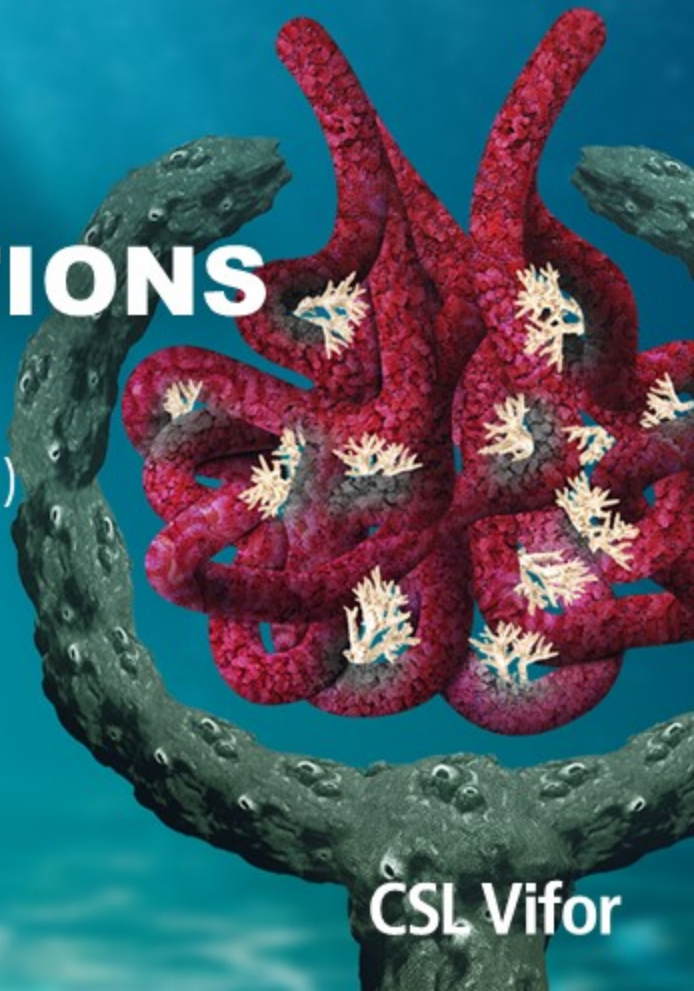
ANG II, angiotensin II; AT_1R, angiotensin II receptor type 1; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; pIgA, polymeric immunoglobulin A

1. Lai KN, *et al. J Am Soc Nephrol* 2003;14:3127–37; **2.** Tamouza H, *et al. Kidney Int* 2012;82:1284–96; **3.** Kobori, *et al. Curr Pharm Des* 2013;19:3033–42; **4.** Ye ZC, *et al. Clin Invest Med* 2009;32:E20–7; **5**. Xing L, *et al. J Int Med Res* 2019;47:5205–15.

Target Proteinuria

ENDOTHELIN-1 AND ANGIOTENSIN II INTERACTIONS

Endothelin-1 (ET-1) and Angiotensin II (ANG II) in IgA Nephropathy (IgAN)



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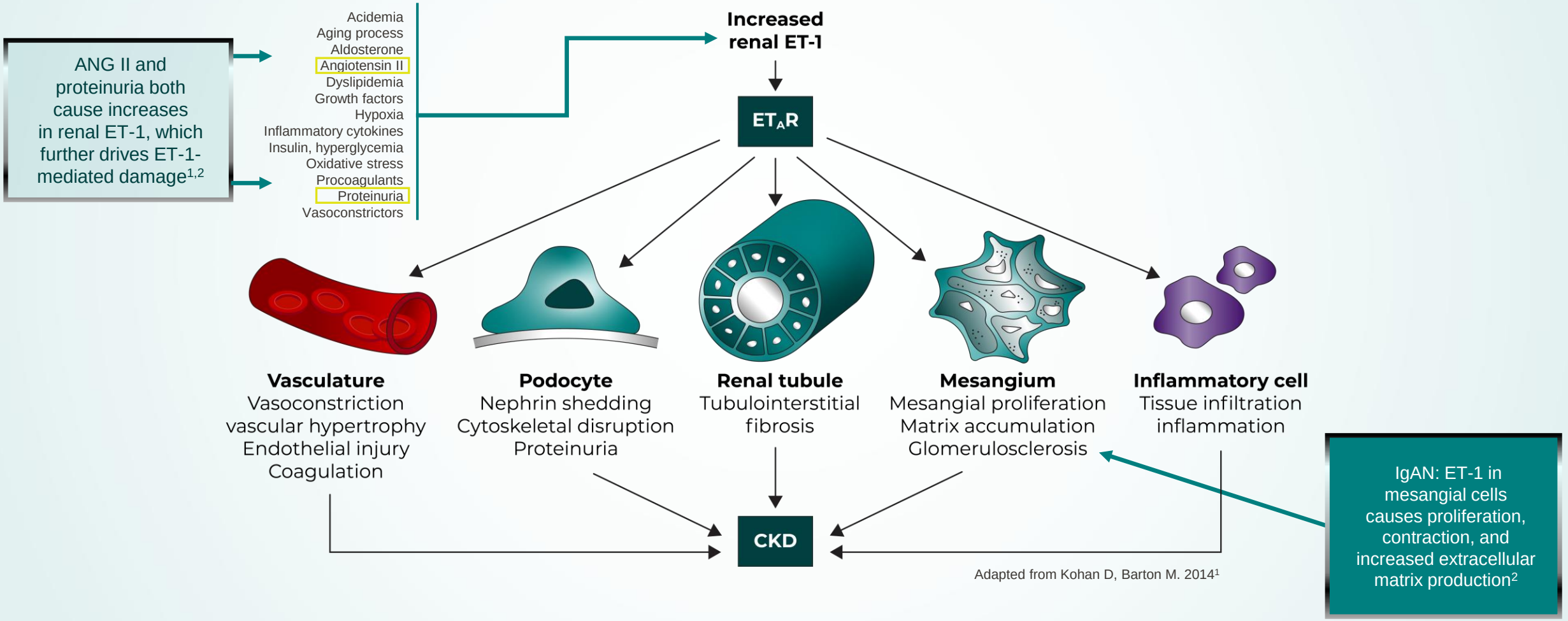
ET-1 AND ANG II INTERACT TO EXACERBATE KIDNEY INJURY



Adapted from Kohan D, Barton M. 2014[1]

ANG II, angiotensin II; ET-1, endothelin-1; ET_AR, endothelin receptor type A; IgAN, immunoglobulin A nephropathy

1. Kohan D, Barton M. *Kidney Int* 2014;86:896–904; 2. Barton M, Sorokin A. *Semin Nephrol* 2015;35:156–67.

ET-1 AND ANG II INTERACT DURING MESANGIAL CELL PROLIFERATION AND MATRIX PROTEIN SYNTHESIS[1]

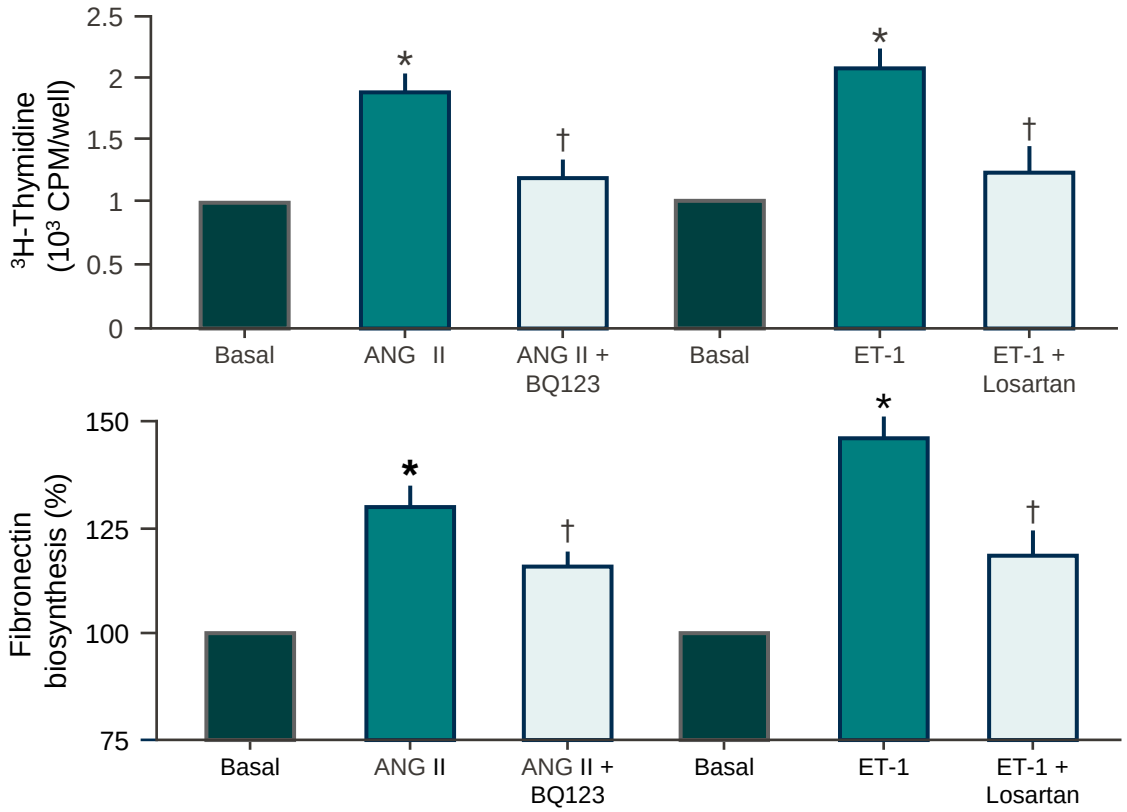
STUDY TYPE AND OBJECTIVE

- Mesangial cells from the glomeruli of male Sprague–Dawley rats were isolated and cultured
- **Objective:** To study the potential interaction between ET-1 and ANG II on fibronectin synthesis and mesangial cell proliferation

KEY RESULTS

- ET_AR antagonism significantly inhibited ANG II–induced mesangial cell proliferation and fibronectin synthesis ($p<0.05$ vs agonist alone)
- AT_1R antagonism significantly inhibited ET-1–induced mesangial cell proliferation and fibronectin synthesis ($p<0.05$ vs agonist alone)

ET-1 and ANG II-induced mesangial cell proliferation and fibronectin synthesis



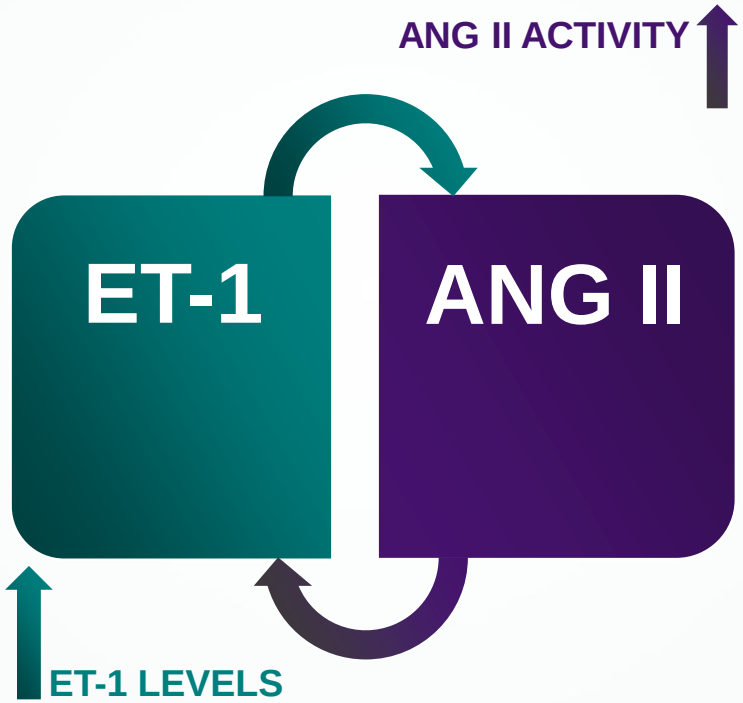
Adapted from Gomez-Garre D, *et al*. 1996[1]

*p<0.05 vs. basal.†P<0.05 vs. agonist alone
ANG II, angiotensin II; AT_1R, angiotensin receptor type 1; CPM, counts per million; ET-1, endothelin-1; ET_AR, endothelin receptor type A

1. Gómez-Garre D, *et al. Hypertension* 1996;27:885–92.

ANG II AND ET-1 INTERACT IN A POSITIVE FEEDBACK LOOP

The ET-1 pathway **impacts ANG II-mediated signalling** through stimulation of **aldosterone secretion**, stimulation of **ANG II formation in pulmonary endothelial cells**, mediation of ANG II **vascular actions**, and **inhibition of renin release** from the juxta glomerular apparatus[1]



ANG II also impacts the ET-1 pathway: **ANG II stimulates ET-1 release** in a variety of cells, including renal cells, creating a positive feedback loop between the **signalling pathways**,[1,2] and ANG II enhances ET-1-induced **vasoconstriction** via **upregulation** of endothelin receptor type A (**ET_AR**) expression and **ET-1–ET_AR binding**[3]

ANG II, angiotensin II; ET-1, endothelin-1, ET_AR, endothelin receptor type A

1. Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol.* 2016;310:R877–84. **2.** Kohan DE, Barton M. *Kidney Int.* 2014;86:896–904. **3.** Lin YJ, *et al. Biochem Biophy Res Commun.* 2014;451:263–9.

ANG II MODULATES ET-1 PROTEIN TISSUE CONTENT THROUGH ET_AR-COUPLED MECHANISMS[1]

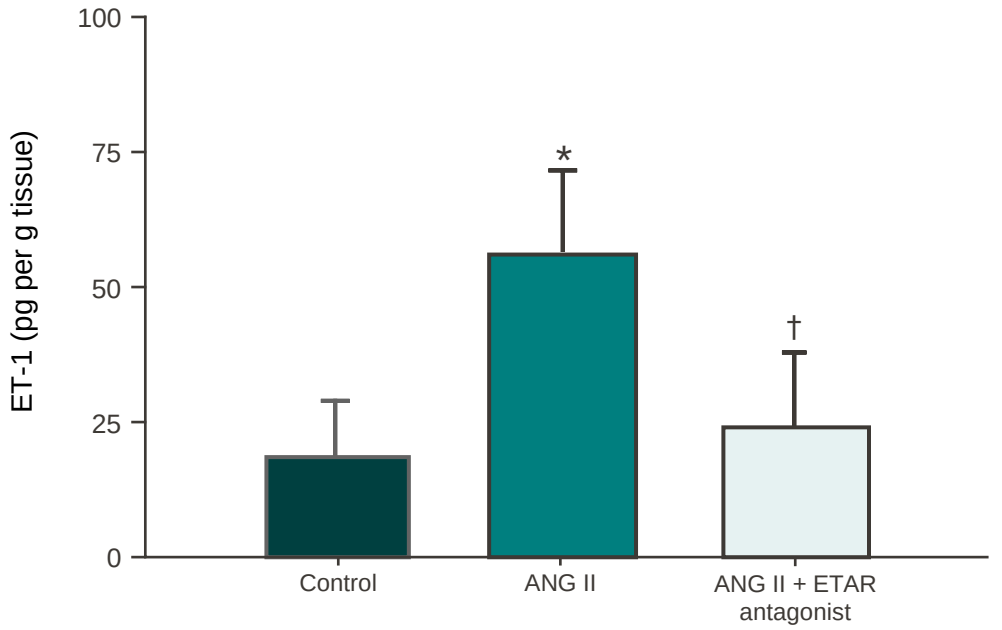
STUDY TYPE AND OBJECTIVE

- Wistar–Kyoto rats were divided into 3 groups and treated for 2 weeks with ANG II, saline, or ANG II + ET_AR antagonist
- **Objective:** Investigate the effects of ANG II, with or without ET_AR antagonism, on ET-1

KEY RESULTS

- ANG II increased ET-1 protein in the kidneys 3-fold compared with controls ($p<0.05$)
- ANG II-mediated increase in ET-1 was significantly inhibited by ET_AR antagonism ($p<0.05$)

EFFECT OF ANG II ON ET-1 LEVELS IN THE KIDNEY



Adapted from Barton M, *et al*. 1997[1]

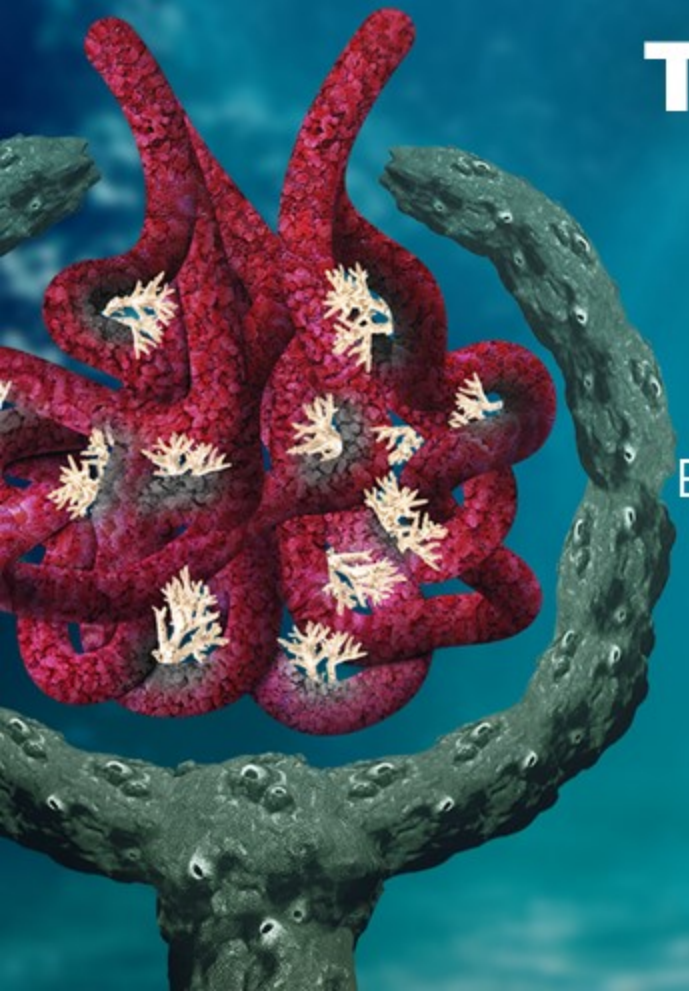
*$p<0.05$ vs control. †$p<0.05$ vs ANG II
ANG II, angiotensin II; ET-1, endothelin-1, ET_AR, endothelin receptor type A

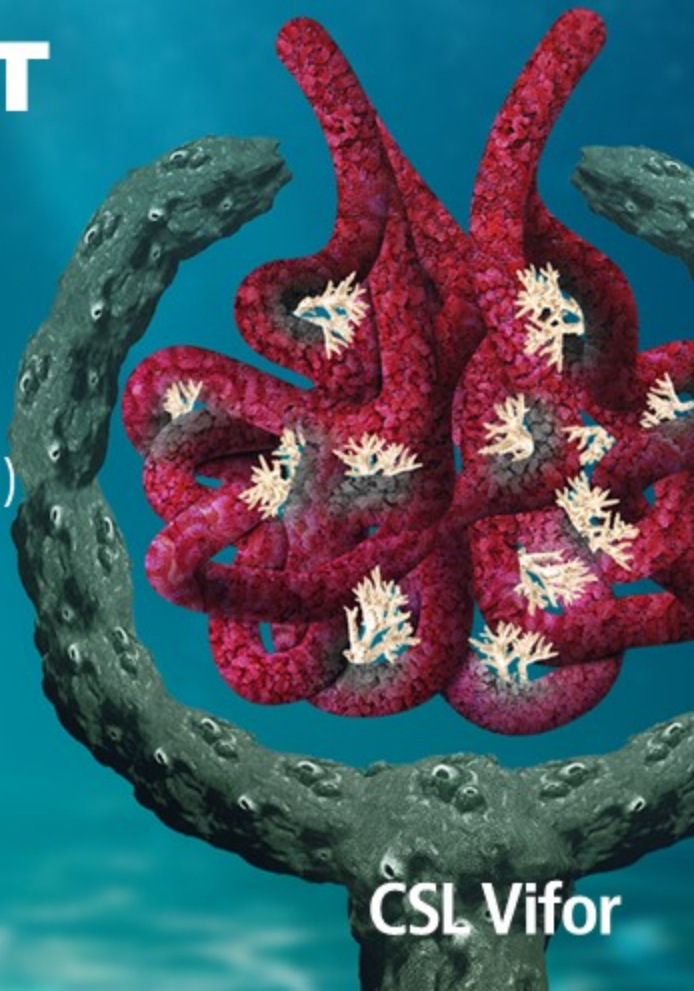
1. Barton M, *et al. Biochem Biophys Res Commun* 1997; 238:861–5.

Target Proteinuria

THE COMBINED EFFECT OF ENDOTHELIN-1 AND ANGIOTENSIN II

Endothelin-1 (ET-1) and Angiotensin II (ANG II) in IgA Nephropathy (IgAN)





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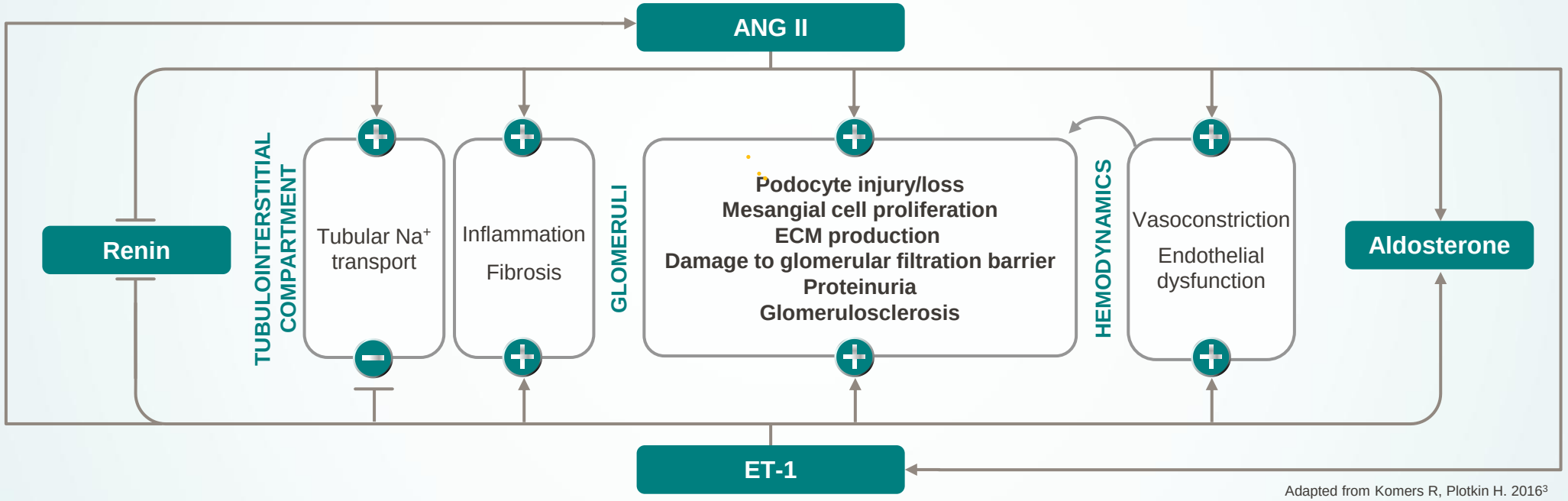
ET-1 AND ANG II ACT IN TANDEM TO AMPLIFY DAMAGE THROUGH MULTIPLE PATHOPHYSIOLOGIC PROCESSES

Pathophysiologic actions of ET-1 and ANG II in the kidney



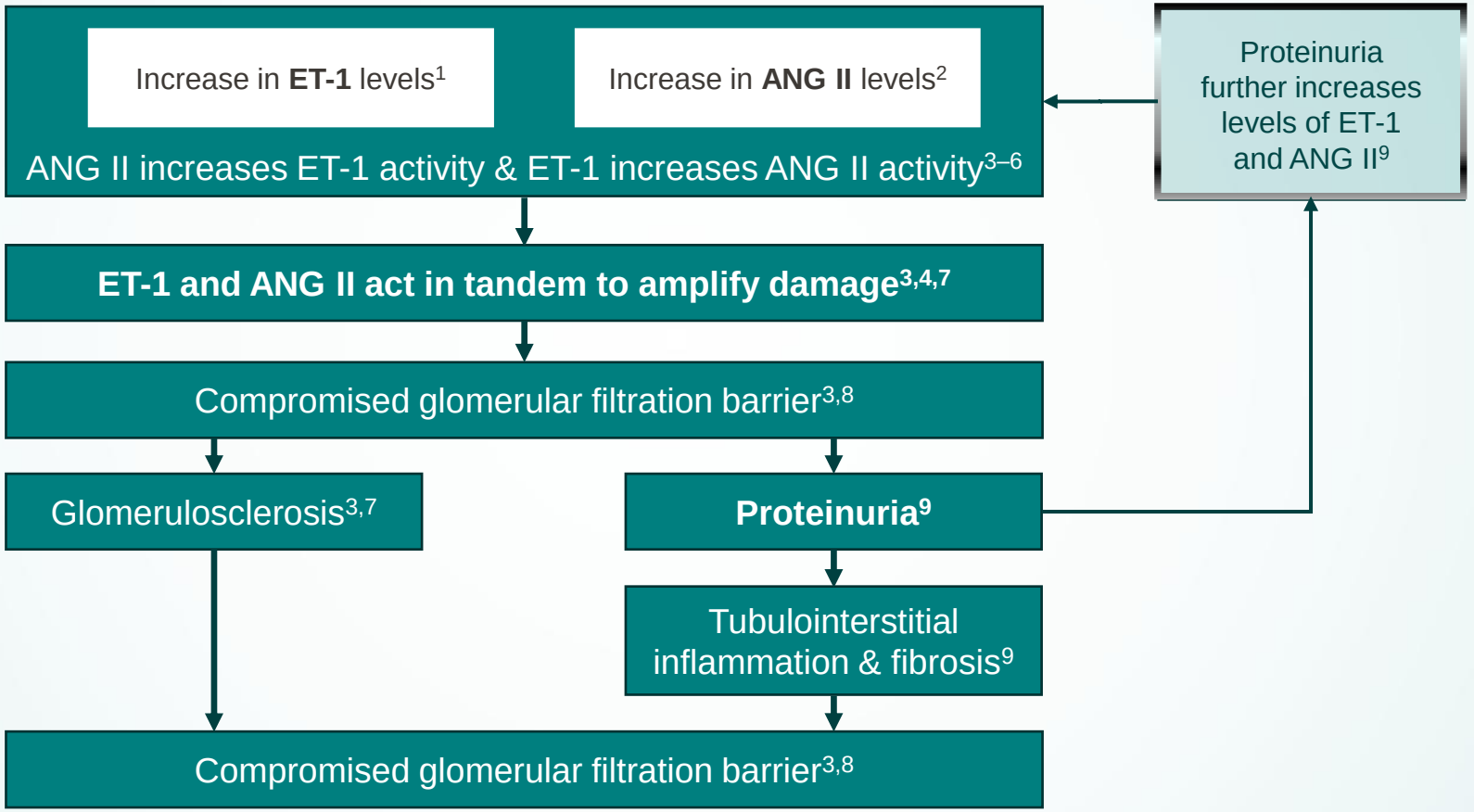
Adapted from Komers R, Plotkin H. 2016[3]

ET-1 and ANG II act in tandem to amplify the inflammatory cytokine response and potentiate glomerular dysfunction, tubulointerstitial injury, and vascular dysfunction, worsening proteinuria and resulting in a progressive decline in kidney function[1–3]

ANG II, angiotensin II; ECM, extracellular matrix; ET-1, endothelin-1

1. Siragy H, Carey R. *Am J Nephrol* 2010;31:541–50; **2.** Ruiz-Ortega M, *et al. Nat Rev Nephrol* 2020;16:269–88. **3.** Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol.* 2016; 310:R877–84.

TOGETHER ET-1 AND ANG II LEAD TO THE PROGRESSIVE LOSS OF KIDNEY FUNCTION, AND ULTIMATELY KIDNEY FAILURE



ANG II, angiotensin II; ET-1, endothelin-1

1. Lehrke I, *et al. J Am Soc Nephrol.* 2001;12(11):2321–9; **2.** Chan LY, *et al. J Am Soc Nephrol.* 2005;16(8):2306–17; **3.** Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol.* 2016;310:R877–84; **4.** Kohan DE, Barton M. *Kidney Int.* 2014;86:896–904; **5.** Benigni A, *et al. Pediatr Nephrol.* 2021;36(4):763–75; **6.** Lin YJ, *et al. Biochem Biophy Res Commun.* 2014;451:263–9; **7.** Raina R, *et al. Kidney Dis.* 2020;6:22–34; **8.** Kohan DE, *et al. Compr Physiol.* 2011;1(2):883–919; **9.** Sharma S, Smyth B. *Kidney Blood Press Res.* 2021;46(4):411–20.

- Both **ET-1 and ANG II** are implicated in the **pathophysiology of IgAN**
- ET-1 via ET_AR, and ANG II via AT_1R interact in a **positive feedback loop to exacerbate kidney damage**
- The **combined effect of ET-1 and ANG II** amplifies the inflammatory cytokine response, glomerular dysfunction, tubulointerstitial injury, and vascular dysfunction, **worsening proteinuria** and resulting in a **progressive decline in kidney function**

ANG II, angiotensin II; AT_1R, angiotensin II receptor type 1; ET-1, endothelin-1, ET_AR endothelin receptor type A; IgAN, immunoglobulin A nephropathy